Remarks

Claims 1-8 are pending in the subject application and are currently before the Examiner. Applicants gratefully acknowledge the Examiner's withdrawal of the previous rejection under 35 USC §112, first paragraph. Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants note that a Claim of Priority Under 35 USC §119 (a copy of which is attached with this Response for the Examiner's convenience) was included with the filing materials when the subject application was submitted to the Patent Office on August 10, 2001. In accordance with MPEP 201.14(b), Applicants reaffirmed their claim to foreign priority and requested that the foreign priority applications from the parent application, U.S. application Serial No. 08/792,415 (hereinafter the '415 application), be made of record in the subject application. Applicants note that certified copies of Great Britain priority applications Serial No. 9602174.6 and 9618836.2 were submitted to the Patent Office in the '415 application on June 4, 1997. Applicants further note that the Examiner in the '415 application acknowledged receiving all of the certified copies of the priority documents under 35 USC §119 on the Office Action Summary page dated November 27, 1998. Accordingly, Applicants respectfully request acknowledgment in the next Communication from the Patent Office of their claim to foreign priority and that the foreign priority documents have been made of record by the Examiner in the subject application.

Claims 1-3, 6, and 8 are rejected under 35 USC §103(a) as obvious over Shaflee (1969) in view of Barry (1993) or Miller (1980) and Miller (U.S. Patent No. 4,254,261). In addition, claims 1-6 and 8 are rejected under 35 USC §103(a) as obvious over Shaflee (1969) in view of Barry (1993) or Miller (1980) and Miller (U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880). Further, claims 1-8 are rejected under 35 USC §103(a) as obvious over Shaflee (1969) in view of Barry (1993) or Miller (1980) and Miller (U.S. Patent No. 4,254,261) further in view of Rometsch (U.S. Patent No. 2,957,880) and further in view of Jacques (1981) supplemented with Harris (U.S. Patent No. 6,242,464). Applicants respectfully traverse these grounds of rejections.

Applicants respectfully maintain that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. Under the §103

rejection in the initial Office Action (dated September 28, 2001) in the subject application, the Examiner made the following statements concerning the teachings of the cited references:

> Determination of the scope and content of the prior art (MPEP §2141.01)
> Shaflee et al. disclosed process of making single R,R-threo-methylphenidate (see abstract last three lines).
>
> Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)
> Shaflee et al. Disclosed all the elements of the claims **except** that a further racemisation step was not included. Barry taught that in preparation of amino acid esters analogous to the claims, racemisation of such ester is achieved under acidic conditions (see acetic acid) and recycling through racemization of the other isomer would give more of the intended isomer (see Miller Ca94 and '261 col.1 line 64-66).
>
> Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)
> One having ordinary skill in the art is deemed to be aware of all the pertinent art in the field. The above references placed the single enantiomer, process of making and alternative choices for increasing single isomeric form in the possession of artisan in the field. It would have been prima facie obvious to employ a conventional modification of Barry or Miller for the conventional process of Shaflee **because** producing higher yield of a desirable single isomer is expected which are the attributes taught by prior art. (emphasis added)

Applicants acknowledge that the Shaflee reference discloses methylphenidate, a known compound having two stereogenic centers. However, the Shaflee reference does not teach or suggest methods for racemizing methylphenidate at both of the chiral centers in the molecule, so that every one of the four possible stereoisomers of methylphenidate is produced. Applicants note that the Examiner states in the instant Office Action that the Shaflee reference teaches "... stereogenic methylphenidate, stereogenic resolution pheniramine with achiral acid ..." (emphasis added). The Examiner's reference in the Office Action to the Shaflee reference as teaching "resolution" suggests that the Examiner may have confused certain technical aspects of Applicants' claimed invention. Resolution of a compound is not the same thing as racemization; in fact, resolution of a chiral compound is the opposite of racemization of a chiral compound. In resolution, one goes from racemate to optical enrichment, whereas in racemization, one goes from enantiomeric excess to racemate. The Shaflee reference does **not** teach (nor do any of the other references cited by the Examiner teach) **racemization** of methylphenidate to produce all four stereoisomers. Prior to

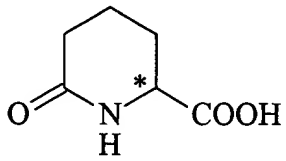
Applicants' surprising discovery, the prior art did not teach or suggest, and the ordinarily skilled artisan did not have a reasonable expectation of being able to **racemize methylphenidate at both chiral centers** of the molecule. None of the other references cited by the Examiner teach or suggest racemization of methylphenidate, or an analogous compound, at both of the chiral centers in the molecule, so that every one of the four possible stereoisomers is produced. In fact, none of the other references teach or suggest a compound that has two chiral centers within the molecule itself.

Although it is not clear from the Examiner's comments in the Office Actions, the Examiner may have assumed that if one uses the racemization methods described in the cited references to racemize a methylphenidate enantiomer, then racemization will occur at both chiral centers of the methylphenidate molecule so as to produce all four possible stereoisomers. With all due respect to the Examiner, Applicants respectfully assert that this assumption is incorrect. Applicants further note that the Examiner's remarks regarding racemization were made without providing any evidence or cited references which teach or suggest how an ordinarily skilled artisan might effect racemization of methylphenidate at both chiral centers. As evidence that the prior art does not teach or suggest means to racemize methylphenidate at both of its chiral centers, one need look no farther than the cited Rometsch patent. Although Example 6 of the Rometsch patent discloses epimerisation of methylphenidate with base, only one of the two chiral centers of the molecule is racemized, with the result being a mixture of diastereomers (*i.e.*, that less than all of the four possible stereoisomers are produced). Thus, Applicants respectfully assert that not only does the prior art not teach or suggest a means for racemization of a single enantiomer of methylphenidate wherein all four stereoisomers of methylphenidate are obtained, the cited Rometsch patent actually teaches away from Applicant's claimed invention in that it teaches racemization of methylphenidate that occurs at only one of the two chiral centers of the molecule. If the substrate is racemized at only one chiral center, the product of racemization does not contain the enantiomer that is the specified product of claim 1 and, therefore, the racemization procedure is unsuitable for the process as claimed in the subject application.

The claims in the subject application specifically recite that racemization results in a mixture of all four possible stereoisomers of methylphenidate (*i.e.*, *d-erythro*-methylphenidate, *l-erythro*-methylphenidate, *d-threo*-methylphenidate, and *l-threo*-methylphenidate stereoisomers).

Consideration of the molecular structure of methylphenidate would suggest to the ordinarily skilled artisan that one chiral center can be racemized much more easily than the other, thereby leading to production of fewer than all four possible stereoisomers. This is borne out by the experimental evidence in the Rometsch patent. Applicants respectfully assert that, at the time of the present invention, racemization methods to produce all four stereoisomers from a single enantiomer of methylphenidate were not taught or suggested in the art. None of the cited references teach or suggest racemization methods that produce all four stereoisomers from a single enantiomer of methylphenidate. The effectiveness of Applicants' claimed invention in racemizing methylphenidate is, therefore, surprising.

The Examiner appears to rely on the Miller and Barry references as teaching means for racemizing single enantiomer methylphenidate in accordance with Applicants' claimed process. Applicants acknowledge that the Miller and Barry references do disclose racemization of a cyclic amino acid (specifically, 6-oxo-2-piperidine carboxylic acid) and an amino acid ester, respectively. In regard to the Miller reference cited by the Examiner, Applicants respectively assert that the compound to be resolved by Miller is represented by the following formula, wherein the * represents a chiral center:

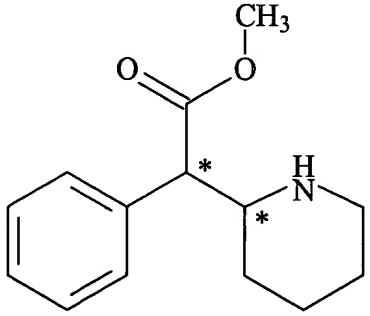


Applicants respectfully request that the Examiner note that the above compound has only **one chiral center** within the molecule itself. In the instant Office Action, the Examiner also cites the Miller reference as teaching ". . . aminoadipic acid wherein two stereogenic center are found in the salt (line 54)." Applicants respectfully assert that aminoadipic acid also has only **one chiral center** within the molecule itself. In the instant Office Action, the Examiner refers to an example wherein "... the two stereogenic centers are from methylphenidate and the 'resolution agent' ...." Thus, the Examiner appears to assume that Applicants' remarks directed to the fact that there are two chiral centers in methylphenidate also encompass the situation where one center is in the compound and another center is in the resolving agent (such that the salt has "one center" plus "another center" and this equals "two stereogenic centers"). This is not the case. Applicants respectfully reemphasize that

their claimed process involves racemization of a compound (methylphenidate) in which there are two chiral centers in the molecule itself such that the end result of the racemization is the production of all four possible stereoisomers of the racemized molecule. The claimed process is possible only because of Applicants' discovery of means to effect **racemization** of **both of the chiral centers** that are present in a **single molecule of methylphenidate**.

In the Office Action dated September 28, 2001, the Examiner stated that the Barry reference taught "preparation of amino acid esters analogous to the claims ..." and racemization of the amino acid esters. As Applicants have stated in their previous response and maintain herein, the substrates in the Barry reference have only **one chiral center** within the molecule itself. Thus, any racemization that may be taught in the Barry reference is racemization of a molecule with a single chiral center, not racemization of a molecule with two chiral centers as in Applicants' claimed invention.

In contrast, methylphenidate has the following structure, wherein each * represents a chiral center:



As noted previously, methylphenidate has **two chiral centers**. As can be understood from the above, the compounds described in the Miller and Barry references only have one chiral center within the molecule itself; methylphenidate has two chiral centers. Therefore, the amino acid esters taught in Barry and the compound taught in Miller are **not analogous** to methylphenidate. As discussed at page 2, lines 8-9, of the subject specification, the subject invention is based on the surprising discovery of means to effect racemization of both chiral centers of methylphenidate. It is only the subject application that teaches means for effectively racemizing a single enantiomer of methylphenidate such that all four stereoisomers are produced. There is no teaching or suggestion in the Miller or Barry references that the racemization methods described therein (which as Applicants

have pointed out were used to racemize compounds with a single chiral center) could be used to successfully racemize single enantiomer methylphenidate at both of its two chiral centers so as to produce all four possible stereoisomers. The Examiner has not provided any scientific basis to support the assertion in the Office Action dated September 28, 2001 that one would only have to employ a "conventional modification" of [the methods of] Barry or Miller to render Applicants' claimed process obvious. Moreover, the Examiner has failed to state in the Office Actions what that "conventional modification" is, or why it would be considered "conventional." As the Examiner is aware, in establishing a *prima facie* case of obviousness, the burden is on the Patent Office to provide an evidentiary basis for asserting logic and scientific principles in support of the rejection. *In re Grose*, 201 USPQ 57 (CCPA 1979). Thus, Applicants respectfully maintain that the Miller and Barry references do not teach or suggest compounds having two stereogenic centers, and Miller and Barry do not teach or suggest means for racemization at both centers of compounds having two stereogenic centers, such as methylphenidate, wherein all of the four possible stereoisomers are produced.

In the instant Office Action, at the end of the remarks concerning the obviousness rejection, the Examiner suggests that Applicants should provide factual evidence "instead of mere arguments" to rebut the obviousness rejection. As the Examiner is aware, it is well established in patent law that in order to support a *prima facie* case of obviousness, a person of ordinary skill in the art must find both the suggestion of the claimed invention, and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Applicants respectfully assert that none of the cited references teach or suggest means for racemization at both of the chiral centers in methylphenidate so as to produce all four possible stereoisomers of the molecule. Applicants have cited factual evidence, not "mere arguments, in support of their position that a *prima facie* case of obviousness is not established by the references cited by the Examiner. Therefore, Applicants' claimed invention is not obvious over the cited references. Should the Examiner disagree and maintain all or some of the rejections, then Applicants respectfully request that the Examiner point out with specificity where the references teach or suggest each and every element of Applicants' claimed method.

In view of the above remarks, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

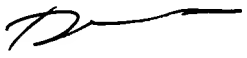
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRP/sl
Attachment: copy of Claim of Priority Under 35 USC §119